

CLAIMS

1. Pharmacologically active compounds of general formula (I)



wherein

Y means the molecular moiety of general formula (Ia), wherein n is an integer from 10 to 400, preferably 20 to 200; one of R₁ and R₂ stands
10 for hydrogen atom whereas the other one means a group of formula (B);



R₃ means a polymerization-initiating group, preferably (CH₃)₂CCN group;
20

W means a hydroxyl group, optionally as a salt formed with an alkali metal ion, preferably sodium ion;

V stands for a C1-8, preferably C4-6, alkylamino group bonded through its amino group;

25 X is a "spacer" group being an amino acid group or an oligopeptide group of at most six members coupled through its N-terminal to the Y group and optionally bearing a hydroxyl group or a valence bond on its C-terminal, wherein the amino acids are Gly, Ala, Leu, Ile, Val, Phe, Tyr, Ahx, Pro, Arg or His;

30 A represents a pharmacologically active polypeptide group containing an amino group and directly coupled therethrough to the Y group when r is 0; or coupled to the C-terminal of the X group, respectively; when r is larger than 0;

r is an integer from 0 to 0.2 n;

35 k is an integer being at most equal to r; is an integer from 0 to (n-r); and

u is an integer from n to 2n-r-z, as well as the salts and complexes of these compounds.

2. Pharmacologically active compounds of general formula (I) as claimed in claim 1, wherein

5 A means a pharmacologically active peptide hormone group coupled through its amino group; and k, r, u, z, X, Y, V and W are as defined in claim 1, as well as the salts and complexes of these compounds.

10 3. Pharmacologically active compounds of general formula (I) as claimed in claim 2, wherein:

A means a native GnRH hormone coupled through its amino group or a pharmacologically active analogue thereof; and k, r, u, z, X, Y, V and W are as defined in claim 1, as well as the salts and complexes of these compounds.

15 4. Pharmacologically active compounds of general formula (I) as claimed in claim 3, wherein

A stands for

20 Glp-His-Trp-Ser-His-Asp-Trp-Lys-Pro-Gly-NH₂,
Ac-D-Trp^{1,3},D-Cpa²,D-Lys⁶,D-Ala¹⁰-GnRH
Ac-D-Trp^{1,3},D-Cpa²,Lys⁵,[Asp(a-DEA)]⁶,D-Ala¹⁰-(Gln⁸-GnRH),
D-Phe²,D-Trp³,D-Lys⁶-GnRH,
Lys⁵,cyclo(Asp⁶-Lys⁸)-GnRH-III,
25 Lys⁴,[Lys(e-Fmoc)]⁸-GnRH-III,
Lys⁴-GnRH-III,
D-Lys⁶-GnRH,
Lys⁵,D-Trp⁶-GnRH

30 coupled to X or Y through the e-amino group of their Lys side chains; and k, r, u, z, X, Y, V and W are as defined in claim 1, as well as the salts and complexes of these compounds.

35 5. Pharmacologically active compounds of general formula (I) as claimed in any of claims 1 to 4, wherein X means an oligopeptide group consisting of four members, preferably -Gly-Phe-Leu-Gly-, and k, r, u, z, A, Y, V and W are as defined in claim 1, as well as the salts and complexes of these compounds.

6. Pharmacologically active compounds of general formula (I) as claimed in any of claims 1 to 4, wherein X means an oligopeptide group consisting of three members, preferably -Phe-Leu-Gly- or -Gly-Leu-Gly-; and k, r, u, z, A, Y, V and W are as defined in claim 1, as well as the salts and complexes of these compounds.

7. Pharmacologically active compounds of general formula (I) as claimed in any of claims 1 to 4, wherein X means an -Ahx- group; and k, r, u, z, A, Y, V and W are as defined in claim 1, as well as the salts and complexes of these compounds.

8. Pharmacologically active compounds of general formula (I) as claimed in any of claims 1 to 4, wherein r is 0; and k, u, z, A, Y, V and W are as defined in claims 1 to 4, as well as the salts and complexes of these compounds.

9. Compounds of general formula (Ic),



wherein Y means the molecular moiety of general formula (Ia), wherein n is an integer from 10 to 400, preferably 20 to 200; one of R₁ and R₂ stands for hydrogen atom whereas the other one means a group of formula (B); R₃ means a polymerization-initiating group, preferably (CH₃)₂CCN group; W means a hydroxyl group, optionally as a salt formed with an alkali metal ion, preferably sodium ion; V' stands for a C1-8, preferably C4-6, alkylamino group bonded through its amino group; X represents an amino acid group or an oligopeptide group of at most six members coupled through its N-terminal to the Y group; OQ means an activated ester group on C-terminal of the X group, preferably ONp, OPcp, Opfp or ONsu group; r is an integer from 0 to 0.2 n; z is an integer from 0 to (n-r); and u is an integer from n to (2n-r-z), as well as the salts of these compounds.

10. Compounds of general formula (Ic) as claimed in claim 9, wherein X means an oligopeptide group consisting of at most four members, preferably -Gly-Phe-Leu-Gly-, -Gly-Phe-Gly-, -Phe-Leu-Gly- or -Ahx-; OQ stands for ONp group; and k, r, u, z, A, Y, V' as well as W are as defined in claim 9, as well as the salts of these compounds.

11. A pharmaceutical composition, which comprises as active ingredient a novel compound of general formula (I) as claimed in any one of claims 1 to 8, wherein k, r, u, z, X, Y, V and W are as defined in any of claims 1 to 8, or a pharmaceutically acceptable salt or complex thereof in admixture with carriers and/or additives commonly used in the pharmaceutical industry.

12. A tumour-inhibiting pharmaceutical composition, which comprises a compound of general formula (I) as claimed in claim 3 or claim 4 or a pharmaceutically acceptable salt or complex thereof in admixture with carriers and/or additives commonly used in the pharmaceutical industry.

13. A tumour-inhibiting and immunostimulatory pharmaceutical composition, which comprises as active ingredient a novel compound of general formula (I), wherein A means Ac-D-Trp^{1,3}, D-Cpa², Lys⁵, [Asp(-DEA)]⁶, D-Ala¹⁰-(Gln⁸-GnRH), and k, r, z, u, X, Y, V and W are as defined in claim 1, or a pharmaceutically acceptable salt or complex thereof in admixture with carriers and/or additives commonly used in the pharmaceutical industry.

14. Compounds of general formula (IV),

$$X-R^1-R^2-R^3-R^4-R^5-R^6-R^7-R^8-Pro-R^{10}-Y \quad (IV)$$

wherein

X means hydrogen, acetyl group or propionyl group when
 5 R^1 is different from pGly; or an intramolecular acid amide bond
 when R^1 stands for pGlu;

R^1 stands for pGlu, Glu, D-Trp, D-Cpa, D-Nal or D-Phe;

R^2 means His, D-Phe or D-Cpa;

R^3 represents D-Cpa, D-Pal or L- or D-Trp optionally
 10 protected on the indolyl moiety;

R^4 stands for Ser; or Lys optionally protected on the ϵ -amino
 group;

R^5 means Tyr; or Lys optionally protected on the ϵ -amino
 group; or His;

15 R^6 stands for Asp, Glu, D-Lys and optionally ϵ -amino
 methylated derivatives thereof; as well as D-Trp, D-Phe, D-Leu, D-
 Ala, D-Cpa or D-Arg;

R^7 represents Phe, Leu or N-Me-Leu; or L-Trp optionally
 protected on the indolyl moiety;

20 R^8 means Lys optionally protected on the ϵ -amino group;
 Arg, Gln; or R^6 and R^8 together can form an intramolecular ring
 through the ϵ -amino group of Lys when R^6 is Asp and R^8 means
 Lys;

R^{10} stands for Gly, D-Ala or a valence bond; and

25 Y represents OH or NH₂ group when R^{10} means Gly or D-Ala;
 or an ethylamide group when R^{10} means a valence bond, as well as
 the pharmaceutically acceptable salts and/or esters of these
 compounds.

30

15. A compound as claimed in claim 14 selected from the
 group consisting of:

[Lys(ϵ -Fmoc)]⁵-GnRH-III,

Lys⁵-GnRH-III,

35 Lys⁵,cyclo[Asp⁶-Lys⁸]-GnRH-III,

Lys⁵,[Lys(ϵ -Fmoc)]⁸-GnRH-III,

Lys⁴,[Lys(ϵ -Fmoc)]⁸-GnRH-III,

Lys⁴-GnRH-III,

[Lys(ϵ -Ac)]⁴-GnRH-III,
 Glu⁶-GnRH-III,
 cyclo[Asp⁶-Lys⁸]-GnRH-III,
 D-Ala¹⁰-GnRH-III,
 5 H-D-Trp¹, [Lys(ϵ -Fmoc)]⁸, D-Ala¹⁰-GnRH-III,
 Ac-D-Trp¹, D-Ala¹⁰-GnRH-III,
 H-D-Trp¹, D-Ala¹⁰-GnRH-III,
 [Trp(For-Ind)]^{3,7}-GnRH-III,
 Phe⁷-GnRH-III,

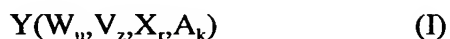
10 GnRH-III(1-9)-ethylamide,
 Lys⁵, D-Trp⁶-hGnRH,
 Lys⁴, D-Trp⁶-hGnRH,
 H-Glu¹, D-Trp⁶-hGnRH,
 Lys⁵, D-Phe⁶-hGnRH(1-9)-ethylamide,
 15 Lys⁴, D-Phe⁶-hGnRH(1-9)-ethylamide,
 Lys⁵, D-Cpa⁶-hGnRH(1-9)-ethylamide;

as well as
 pharmaceutically acceptable salts and esters of these compounds.

20 16. A pharmaceutical composition, which comprises as
 active ingredient a novel compound of general formula (IV), wherein
 R1-R8, R10, X and Y are as defined in claim 14, or a
 pharmaceutically acceptable salt or ester thereof in admixture with
 carriers and/or additives commonly used in the pharmaceutical
 25 industry.

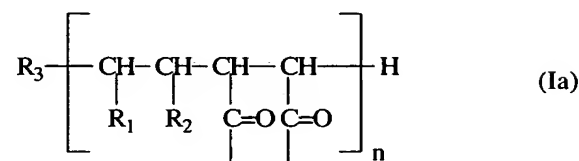
17. A pharmaceutical composition as claimed in claim 16,
 which comprises as active ingredient a compound according to claim
 30 15 or a pharmaceutically acceptable salt or ester thereof.

18. A pharmacologically active compound of formula (I)



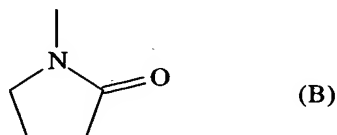
5 wherein

Y represents the molecular moiety of formula (Ia),



wherein n is an integer from 10 to 400; one of R₁ and R₂ represents hydrogen atom whereas the other one represents a group of formula (B);

10



R₃ represents a polymerization-initiating group;

W represents a hydroxyl group, optionally as a salt formed with an alkali metal ion;

15

V represents a C1-8 alkylamino group bonded through its amino group or a valence bond;

X is a "spacer" group being an amino acid group or an oligopeptide group of at most six members wherein the amino acid or oligopeptide group is coupled through its N-terminal to the Y group and is optionally bearing a hydroxyl group or a valence bond on its C-terminal, wherein the amino acids are Gly, Ala, Leu, Ile, Val, Phe, Tyr, Ahx, Pro, Arg, or His;

20

A is present and represents a pharmacologically active polypeptide hormone group containing an amino group and directly coupled therethrough to the Y group when r is 0; or coupled to the C-terminal of the X group, respectively, when r is larger than 0;

25

r is an integer from 0 to 0.2 n;

k is an integer being at most equal to r; z is an integer from 0 to (n-r); and
u is an integer from n to 2n-r-z, as well as the salts and complexes of these
compounds.

5 19. The pharmacologically active compound of formula (I) of claim 18,
wherein R₃ is a (CH₃)₂CCN group.

20. The pharmacologically active compound of formula (I) of claim 19,
wherein:

10 A represents a native gonadotropin-releasing hormone (GnRH) coupled
through its amino group or a pharmacologically active analogue thereof;
and k, r, u, z, X, Y, V and W are as defined in claim 18, as well as the
salts and complexes of these compounds.

15 21. The pharmacologically active compound of formula (I) of claim 20,
wherein

A represents
pGlu-His-Trp-Ser-His-Asp-Trp-Lys-Pro-Gly-NH₂ (SEQ ID NO:2),
Ac-D-Trp^{1,3}, p-chlorophenyl-D-alanine²(D-Cpa²),D-Lys⁶,D-Ala¹⁰-

20 gonadotropin-releasing hormone (GnRH)

Ac-D-Trp^{1,3}, D-Cpa²,Lys⁵,[Asp(a-DEA)]⁶,D-Ala¹⁰-Gln⁸-GnRH,

D-Phe²,D-Trp³,D-Lys⁶-GnRH,

Lys⁵,cyclo(Asp⁶-Lys⁸)-GnRH-III,

Lys⁴,[Lys(ε-Fmoc)]⁸-GnRH-III,

25 Lys⁴-GnRH-III,

D-Lys⁶-GnRH,

Lys⁵,D-Trp⁶-GnRH

coupled to X or Y through the ε-amino group of their Lys side chains; and

k, r, u, z, X, Y, V and W are as defined in claim 18, as well as the salts and
30 complexes of these compounds.

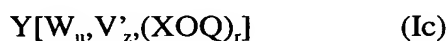
22. The pharmacologically active compound of formula (I) of claim 18, wherein X represents an oligopeptide group consisting of four members; and k, r, u, z, A, Y, V and W are as defined in claim 18, as well as the salts and complexes of these compounds.

23. The pharmacologically active compound of formula (I) of claim 18, wherein X represents an oligopeptide group consisting of three members; and k, r, u, z, A, Y, V and W are as defined in claim 18, as well as the salts and complexes of these compounds.

24. The pharmacologically active compound of formula (I) of claim 18, wherein V is a C4-6 alkylamino group.

25. The pharmacologically active compound of formula (I) of claim 18, wherein r is 0; and k, u, z, A, Y, V and W are as defined in claim 18, as well as the salts and complexes of these compounds.

26. A compound containing an activated ester group of formula (Ic),



wherein Y represents the molecular moiety of formula (Ia), wherein n is an integer from 10 to 400; one of R₁ and R₂ represents hydrogen atom whereas the other one represents a group of formula (B); R₃ represents a polymerization-initiating group; W represents a hydroxyl group, optionally as a salt formed with an alkali metal ion; V' represents a C1-8, alkylamino group bonded through its amino group; X represents an amino acid group or an oligopeptide group of at most six members coupled through its N-terminal to the Y group; OQ represents an activated ester group on C-terminal of the X group; r is an integer from 0 to 0.2 n; z is an integer from 0 to (n-r); and u is an integer from n to (2n-r-z), as well as the salts of these compounds.

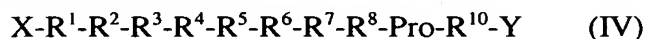
27. Compounds of formula (Ic) as claimed in claim 26, wherein X represents an oligopeptide group consisting of at most four members, preferably -Gly-Phe-Leu-Gly-, -Gly-Phe-Gly-, -Phe-Leu-Gly- or -Ahx-; OQ represents ONp group; and k, r, u, z, A, Y, V' as well as W are as defined in claim 26, as well as the salts of these compounds.

28. A pharmaceutical composition comprising a compound of formula (I) of claim 18, wherein k, r, u, z, X, Y, V and W are as defined in claim 18, or a pharmaceutically acceptable salt or complex thereof in admixture with carriers and/or additives commonly used in the pharmaceutical industry.

29. A tumour-inhibiting pharmaceutical composition comprising a compound of formula (I) of claim 20 or a pharmaceutically acceptable salt or complex thereof in admixture with carriers and/or additives commonly used in the pharmaceutical industry.

30. A tumour-inhibiting and immunostimulatory pharmaceutical composition comprising a compound of formula (I), wherein A represents Ac-D-Trp^{1,3}, p-chlorophenyl-D-alanine²(D-Cpa²), Lys⁵, [Asp(a-DEA)]⁶, D-Ala¹⁰, Gln⁸-GnRH, and k, r, z, u, X, Y, V and W are as defined in claim 18, or a pharmaceutically acceptable salt or complex thereof in admixture with carriers and/or additives commonly used in the pharmaceutical industry.

31. A compound of formula (IV),



wherein

X represents hydrogen, acetyl group or propionyl group when R¹ is different from pGlu; or X is not present when R¹ represents pGlu;

R¹ represents pGlu, Glu, D-Trp, p-chlorophenyl-D-alanine(D-Cpa), D-Nal or D-Phe;

R² represents His, D-Phe, or D-Cpa;

R³ represents D-Cpa, β -(3-pyridyl)-D-alanine(D-Pal) or L- or D-Trp optionally protected on the indolyl moiety;

R⁴ represents Ser; or Lys optionally protected on the ϵ -amino group;

R⁵ represents Tyr; or Lys optionally protected on the ϵ -amino group; or
5 His;

R⁶ represents Asp, Glu, D-Lys and optionally ϵ -amino methylated derivatives thereof; as well as D-Trp, D-Phe, D-Leu, D-Ala, D-Cpa or D-Arg;

R⁷ represents Phe, Leu or N-Me-Leu; or L-Trp optionally protected on the indolyl moiety;

10 R⁸ represents Lys optionally protected on the ϵ -amino group; Arg, Gln; or R⁶ and R⁸ together can form an intramolecular ring through the ϵ -amino group of Lys when R⁶ is Asp and R⁸ represents Lys;

R¹⁰ represents Gly, D-Ala or a valence bond; and

15 Y represents OH or NH₂ when R¹⁰ is Gly or D-Ala; or an ethylamide group when R¹⁰ is a valence bond; or a pharmaceutically acceptable salt or ester thereof.

31. A composition comprising a compound of claim 18 in combination with a pharmaceutically acceptable carrier.

20 32. The pharmacologically active compound of claim 18, wherein n is an integer from 20 to 200.

25 33. The pharmacologically active compound of claim 22, wherein X represents -Gly-Phe-Leu-Gly- (SEQ ID NO:5).

34. The pharmacologically active compound of claim 23, wherein X represents -Phe-Leu-Gly-.

30 35. The pharmacologically active compound of claim 23, wherein X represents -Gly-Leu-Gly-.

36. The compound of claim 26, wherein n is an integer from 20 to 200.
37. The compound of claim 26, wherein R₃ represents (CH₃)₂CCN.
- 5 38. The compound of claim 26, wherein W represents a hydroxyl group as a salt formed with a sodium ion.
39. The compound of claim 26, wherein V' represents a C4-6 alkylamino group.
- 10 40. The compound of claim 26, wherein the activated ester group is selected from the group consisting of ONp, OPcp, Opfp, and ONsu.
- 15 41. A tumour-inhibiting pharmaceutical composition comprising a compound of formula (I) of claim 21 or a pharmaceutically acceptable salt or complex thereof in admixture with carriers and/or additives commonly used in the pharmaceutical industry.